DRAFT External Peer Review Charge Questions for the IRIS Toxicological Review of Formaldehyde—Inhalation

April 2022

Introduction

The U.S. Environmental Protection Agency (EPA) is seeking a scientific peer review of a draft *IRIS Toxicological Review of Formaldehyde—Inhalation* developed in support of the Agency's online database, the Integrated Risk Information System (IRIS). IRIS is prepared and maintained by EPA's Center for Public Health and Environmental Assessment within the Office of Research and Development.

IRIS is a human health assessment program that evaluates scientific information on effects that could result from exposure to specific chemicals or pollutants in the environment. Through IRIS, EPA provides high-quality science-based human health assessments to support the Agency's regulatory activities and decisions to protect public health. IRIS assessments contain information that can be used to support hazard identification and dose-response assessment, two of the four steps in the human health risk assessment process. When supported by available data, IRIS provides health effects information and toxicity values for health effects (including cancer and effects other than cancer) resulting from lifetime exposure. When used by risk managers in combination with information on human exposure and other considerations, IRIS assessments support the Agency's regulatory activities and decisions to protect public health.

An existing IRIS assessment for formaldehyde includes an oral reference dose (RfD) from 1990, and a cancer weight of evidence descriptor and inhalation unit risk (IUR) for cancer from 1991. A draft IRIS formaldehyde assessment was reviewed by the National Academy of Sciences (NAS) in 2011 (NRC, 2011). The IRIS Program decided to conduct a reassessment of formaldehyde inhalation from scratch on the basis of that review, using transparent and predefined systematic review methods. The 2022 draft *Toxicological Review of Formaldehyde—Inhalation* is based on a comprehensive review of the available scientific literature informing the noncancer and cancer health effects in humans exposed to formaldehyde via inhalation, including human and animal health effect studies, as well as extensive mechanistic analyses. Two other documents provide supporting information, the *Supplemental Information to the Toxicological Review of Formaldehyde—Inhalation* (i.e., Appendices) and the *Assessment Overview for the Toxicological Review of Formaldehyde—Inhalation*. The draft assessment was developed according to EPA guidelines and technical reports and contains conclusions on the noncancer human health hazards and carcinogenicity potential posed by formaldehyde inhalation, including a standardized cancer descriptor to express formaldehyde's human carcinogenic potential. The assessment also derives noncancer toxicity values, including a reference concentration (RfC) for lifetime inhalation, and a cancer IUR estimate.

Charge Questions on the Draft Toxicological Review of Formaldehyde—Inhalation

In response to the numbered charge questions below, the advice provided as part of this peer review would be most useful when prioritized to indicate its relative importance as follows:

- **Tier 1:** ***Necessary Revisions*** – Please use this category for any revisions you believe are necessary to adequately support and substantiate the assessment conclusions in the formaldehyde (inhalation) assessment. For Tier 1 recommendations, please clearly describe and justify each necessary revision.
- **Tier 2:** ***Suggested Revisions*** – Please use this category for any revisions you encourage EPA to implement to strengthen the analyses or scientific basis for the assessment conclusions, or to improve the clarity of the presentation in the formaldehyde (inhalation) assessment.
- **Tier 3:** ***Future Considerations*** – Please use this category for any advice you have for scientific exploration that might inform future work. While these recommendations are generally outside the immediate scope or needs of the formaldehyde (inhalation) assessment, they could inform future assessments or research efforts.

1. **Assessment Development Methods and Organization.** The Toxicological Review describes and applies a systematic review process for identifying, screening, and evaluating pertinent studies, and then for prioritizing the evidence to inform hazard and dose-response decisions. This process is described in the Toxicological Review's *Preface on Assessment Methods and Organization*, with documentation primarily in Appendix A.5. Please answer parts (a) and (b).
    a. Please comment on whether the methods for assessment development (*Preface on Assessment Methods and Organization*) and the organization of the assessment are clear and transparent.
    b. Please comment on whether there is sufficient documentation on methods and criteria for the following:
        - Identification of epidemiologic, experimental, and mechanistic studies (please identify any additional peer-reviewed studies that the assessment should consider).
        - Critical evaluation of individual studies or sets of studies.
        - Assessment of the weight of evidence (i.e., evidence integration).
        - Selection of studies and data sets for deriving toxicity values.

2. **Toxicokinetics.** Several assumptions and interpretations were applied in the Toxicological Review that were based on current research (although the draft acknowledges that some uncertainties remain). Please answer parts (a), (b), and (c) considering the extent to which the available science on the toxicokinetics of inhaled formaldehyde is clearly presented and appropriately applied in the assessment of potential respiratory and systemic (i.e., nonrespiratory) health hazards.
    a. Please comment on the Toxicological Review conclusion that inhaled formaldehyde is not likely to be distributed in appreciable amounts beyond the respiratory tract to distal tissues. This conclusion underpins the organization of the assessment and several key assumptions.
    b. Please comment on the Toxicological Review assumptions (based on [a]) that:
        - Inhaled formaldehyde is not directly interacting with tissues distal to the portal-of-entry (POE) to elicit systemic effects.

- Formaldehyde levels in the blood or at systemic sites are not appreciably changed as a result of formaldehyde from exogenous sources (inhalation).
- Inhaled formaldehyde does not cause appreciable changes in normal metabolic processes associated with formaldehyde in distal tissues. Therefore, studies examining potential associations between levels of formaldehyde or formaldehyde byproducts in tissues distal to the POE (e.g., formate in blood or urine; brain formaldehyde levels) and health outcomes are not considered relevant to interpreting the human health hazards of inhaled formaldehyde.

c. Please comment on the Toxicological Review evaluation of considerations regarding endogenous formaldehyde in assessing the health risk due to inhaled formaldehyde.

3. **Respiratory System Health Effects (Noncancer).** For each noncancer POE health effect considered in the assessment and outlined in (a) to (e), below, please comment on whether the evidence integration decisions for hazard identification are clearly described and scientifically justified (considering the extent to which the available data have been appropriately synthesized to describe the strengths and limitations). In addition, please separately comment on whether the dose-response decisions are transparent and scientifically justified, including study selection for dose-response analyses; point of departure (POD) estimates, including modeling choices and assumptions, and dosimetric adjustments; selection of uncertainty factors and derivation of candidate values; selection of organ- or system-specific RfCs (osRfCs); and confidence in the calculated values. For these well-studied health effects, confidence was consistently judged as either *medium* or *high*.

a. Sensory irritation
   - The assessment concludes that the **evidence demonstrates** that inhalation of formaldehyde causes increased sensory irritation in humans, given appropriate exposure circumstances. Well-conducted studies in humans and animals support this hazard conclusion, and strong mechanistic evidence provides a plausible mode of action (MOA) for the identified outcome.
   - A POD from Hanrahan et al. (1984), a human study, was ultimately selected to calculate an osRfC of 0.009 mg/m^3 for eye irritation. A composite uncertainty factor (UF_C) of 10 was applied to address intraspecies uncertainty (UF_H). The assessment also considers PODs from controlled human exposure studies and discusses their utility for developing an RfC for lifetime exposure as well as their potential increased utility for purposes outside the scope of the current assessment (e.g., derivation of an acute RfC).

b. Pulmonary function
   - The assessment concludes that the available **evidence indicates** that long-term formaldehyde inhalation likely causes decreased pulmonary function given appropriate exposure circumstances. This conclusion was supported primarily by evidence in exposed humans, with supportive mechanistic evidence indicating that formaldehyde inhalation results in biological changes related to this outcome.
   - The assessment concludes that the available evidence is inadequate to determine whether acute or short-term (hours to weeks) formaldehyde inhalation might cause decreased pulmonary function in humans.

- A POD from Krzyzanowski et al. (1990), a human study, was ultimately selected to calculate an osRfC of 0.007 mg/m^3 for pulmonary function. A UF_C of 3 was applied to address UF_H. This UF_H value was selected using an evidence-based analysis.

c. Allergy-related conditions
   - The assessment concludes that the available **evidence indicates** that formaldehyde inhalation likely causes increased allergic responses in humans, given appropriate exposure circumstances. This conclusion was supported primarily by evidence in exposed humans, with supportive mechanistic evidence indicating that formaldehyde inhalation results in biological changes related to this outcome.
   - A POD from Annesi-Maesano et al. (2012), a human study, was ultimately selected to calculate an osRfC of 0.008 mg/m^3 for allergy-related conditions. A UF_C of 3 was applied to address UF_H. This UF_H value was selected using an evidence-based analysis.

d. Prevalence of current asthma and degree of asthma control
   - The assessment concludes that the available **evidence indicates** that formaldehyde inhalation likely causes an increased frequency of current asthma symptoms or difficulty controlling asthma, given the appropriate exposure circumstances. This conclusion was supported primarily by evidence in exposed humans, with supportive mechanistic evidence indicating that formaldehyde inhalation results in biological changes related to these outcomes.
   - PODs from the Annesi-Maesano et al. (2012), Krzyzanowski et al. (1990), and Venn et al. (2003) human studies were ultimately selected to calculate an osRfC of 0.006 mg/m^3 for current asthma or degree of asthma control. A UF_C of 3 or 10 was applied to address UF_H. The UF_H value applied to the POD from Annesi-Maesano et al. (2012) was selected using an evidence-based analysis.

e. Respiratory tract pathology
   - The assessment concludes the **evidence demonstrates** that inhalation of formaldehyde causes respiratory tract pathology in humans, given appropriate exposure circumstances. Well-conducted studies in humans and animals support this hazard conclusion, and strong mechanistic evidence in animals provides a plausible MOA for the identified outcomes.
   - PODs from the Kerns et al. (1983) and Woutersen et al. (1989) rat studies were ultimately selected to calculate an osRfC of 0.003 mg/m^3 for squamous metaplasia. The PODs were estimated using dosimetric simulations of formaldehyde flux to the nasal lining using a computational fluid dynamics model to extrapolate from results in rats to humans. A UF_C of 30 or 100 was applied to address UF_H, subchronic (UF_S) and interspecies (UF_A) uncertainties.

4. **Systemic (i.e., nonrespiratory) Health Effects (Noncancer).** For each noncancer systemic health effect considered in the assessment and outlined in (a) to (c), below, please comment on whether the evidence integration decisions for hazard identification are clearly described and scientifically justified (considering the extent to which the available data have been appropriately synthesized to describe the strengths and limitations). In addition, please separately comment on whether the dose-response decisions are transparent and scientifically

justified, including study selection for dose-response analyses; POD estimates, including modeling choices and assumptions, and dosimetric adjustments; selection of uncertainty factors and derivation of candidate values; selection of osRfCs; and confidence in the calculated values. Confidence was consistently lower for these effects as compared with POE effects.

a. Female reproductive or developmental toxicity:
   - The assessment concludes that the **evidence indicates** that inhalation of formaldehyde likely causes female reproductive or developmental toxicity, given appropriate exposure circumstances. The conclusion for female reproductive or developmental toxicity is supported by evidence in humans, specifically, increases in time-to-pregnancy (TTP) and spontaneous abortion risk; mechanistic evidence explaining such effects without systemic distribution of formaldehyde is lacking.
   - A POD from Taskinen et al. (1999), a human study, was ultimately selected to calculate an osRfC of 0.01 mg/m^3 for TTP. A UF_C of 10 was applied to address UF_H and UF_S.

b. Male reproductive toxicity
   - The assessment concludes that the **evidence indicates** that inhalation of formaldehyde likely causes reproductive toxicity in men, given appropriate exposure circumstances. The conclusion for male reproductive toxicity is supported primarily by coherent evidence of several alterations to the male reproductive system in animals exposed to very high levels of formaldehyde (>6 mg/m^3), with some corroborative changes in an occupational epidemiological study; although no MOA is available, some relevant mechanistic changes have been observed in well-conducted studies.
   - A POD from Özen et al. (2002), a rat study, was ultimately selected to calculate an osRfC of 0.01 mg/m^3 for testis weight. A UF_C of 3,000 was applied to address UF_H, LOAEL (UF_L), UF_S, and UF_A.

c. Nervous system toxicity
   - While many studies reporting evidence of potential neurotoxic effects were available, due to limitations identified in the database (e.g., poor methodology, lack of consistency), it was ultimately determined that the **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might pose a human nervous system hazard. This judgment was separately arrived at for three different manifestations of potential neurotoxicity, namely developmental neurotoxicity, altered neurobehavior, and an increased incidence of, or mortality from, the motor neuron disease amyotrophic lateral sclerosis. The evidence integration narrative emphasizes that additional study is warranted.
   - The available data on potential nervous system effects were considered insufficient for developing quantitative toxicity estimates.

5. **Noncancer RfC.** An RfC was selected based on the grouping of osRfCs for sensory irritation, decreased pulmonary function, allergy-related conditions, and increased prevalence of current asthma or decreased degree of asthma control. Please comment on whether the approach and selection of the proposed RfC was clear and scientifically justified, including consideration of other potentially sensitive health effects.

6. **Cancer.** The assessment concludes that formaldehyde is ***Carcinogenic to Humans by the Inhalation Route of Exposure***. Please comment on whether the judgments in (a) to (f), below, are clearly described and scientifically justified. Note that the three judgments in (a), (b), and (c) outline the primary evidentiary support, and that each of these judgments would independently substantiate the carcinogenicity conclusion.

    a. The **evidence demonstrates** that formaldehyde inhalation causes nasopharyngeal cancer (NPC) in humans, based primarily on observations of increased risk of NPC in groups exposed to occupational formaldehyde levels and supported by the evidence of nasal cancers in animals, with strong, reliable, and consistent mechanistic evidence in both animals and humans, including support for a mutagenic MOA.

    b. The **evidence demonstrates** that formaldehyde inhalation causes sinonasal cancer (SNC) in humans, based primarily on observations of increased risk of SNC in groups exposed to occupational formaldehyde levels and supported by the evidence of nasal cancers in animals and consistent mechanistic evidence.

    c. The **evidence demonstrates** that formaldehyde inhalation causes an increased risk of myeloid leukemia in humans, based primarily on observations of increased risk in groups exposed to occupational formaldehyde levels. This judgment is supported by other studies of human occupational exposure that provide strong and coherent mechanistic evidence identifying clear associations with additional endpoints relevant to lymphohematopoietic (LHP) cancers, including an increased prevalence of multiple markers of mutagenicity and genotoxicity in peripheral blood cells of exposed workers, other perturbations to immune cell populations in blood (primarily from human studies). Generally, evidence supporting the development of LHP cancers after formaldehyde inhalation has not been observed in experimental animals (i.e., rodents), including a well-conducted, chronic cancer bioassay in two species, a similar lack of increased leukemias in a second rat bioassay, and multiple mechanistic evaluations of relevant biological changes such as genotoxicity in systemic tissues of exposed rodents. The lack of findings in animals does not detract from the strong human evidence.

    d. The overall conclusion on the carcinogenicity of inhaled formaldehyde was independently supported by the three sets of evidence outlined in 6a-6c above. This carcinogenicity conclusion was not influenced by the judgments for several other cancer types. Specifically, the **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause oropharyngeal/hypopharyngeal cancer, Hodgkin lymphoma, or multiple myeloma in humans; there is **inadequate evidence** to determine whether formaldehyde inhalation may be capable of causing laryngeal cancer or lymphatic leukemia in humans.

    e. Formaldehyde is genotoxic in several test systems and operates, at least in part, through a mutagenic MOA. Specifically, a mutagenic MOA was identified in association with the development of nasal (i.e., nasopharyngeal and sinonasal) cancers, while no MOA was identified for other cancer types. The mechanistic evidence was sufficient to conclude that both mutations and cellular proliferation play a role in nasal carcinogenesis.

    f. The MOA(s) leading to cancer formation outside of the respiratory tract are unknown.

7. **Inhalation unit risk for cancer.** An IUR for cancer is derived on the basis of nasal cancers using data on nasopharyngeal cancers (NPCs) in a human study from the National Cancer Institute (NCI), specifically the results reported in (Beane Freeman et al., 2013). In addition, comparative estimates are provided on the basis of modeling of nasal tumors in exposed rodents. Finally, although not included in the draft IUR, an estimate for myeloid leukemia is presented. Please comment on the clarity and scientific justification for each specific decision in the draft cancer dose-response analyses outlined in (a) to (d), below, including study selection; POD estimates, including modeling choices and assumptions, dosimetric adjustments, and extrapolations; any other adjustments; and confidence in the calculated values. Part (e) includes a specific, additional question on myeloid leukemia.

    a. The NCI study results on NPCs were ultimately selected and used to develop the draft IUR estimate. A lifetable analysis was used to develop a POD and, given the mutagenic MOA for this cancer type, a linear extrapolation was applied. Age-dependent adjustment factors (ADAFs) were applied to this estimate, in accordance with EPA guidelines when a mutagenic MOA is supported. Confidence in the IUR is *medium.*

    b. As a comparison for the modeling of the human data, data from two chronic rat bioassays were used to develop an estimate of nasal cancer risk. Multiple models, including a biologically-based dose-response model, were evaluated and used to extrapolate the results in rats to a POD in humans. A linear extrapolation was applied based on a directly mutagenic MOA for formaldehyde. Furthermore, a candidate RfC based on cell proliferation was also developed for comparison.

    c. For sinonasal cancer, the draft draws an evidence integration judgment of **evidence demonstrates**. Given the lack of quantifiable data to allow the use of dose-response information to identify a POD, the IUR does not incorporate potential contributions to risk for sinonasal cancer. Please comment on this decision and, if this is not supported, include a recommended method to account for this cancer risk.

    d. For myeloid leukemia, a unit risk estimate is presented using the NCI study results (Beane-Freeman et al., 2009). In line with recommendations from the NAS (NRC, 2011), this reassessment draws hazard conclusions and derives a unit risk estimate at the most specific cancer type supported by the available data. The selected data set used to derive the myeloid leukemia estimate combined the results from myeloid leukemia with results for other/unspecified leukemias. ADAFs were not applied to this estimate, as the assessment concludes that the MOA is unknown.

    e. Although the draft concludes that the **evidence demonstrates** that formaldehyde inhalation causes myeloid leukemia, the only data available to develop a unit risk estimate for myeloid leukemia are uncertain. The draft Toxicological Review discusses the strengths and limitations of the myeloid leukemia estimate in detail. Please comment specifically on how the unit risk estimate for myeloid leukemia should inform the IUR for cancer, if at all.

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Beane Freeman, LE; Blair, A; Lubin, JH; Stewart, PA; Hayes, RB; Hoover, RN; Hauptmann, M. (2013). Mortality from solid tumors among workers in formaldehyde industries: an update of the NCI cohort. Am J Ind Med 56: 1015-1026. http://dx.doi.org/10.1002/ajim.22214

Hanrahan, LP; Dally, KA; Anderson, HA; Kanarek, MS; Rankin, J. (1984). Formaldehyde vapor in mobile homes: A cross sectional survey of concentrations and irritant effects. Am J Public Health 74: 1026-1027. http://dx.doi.org/10.2105/ajph.74.9.1026

Kerns, WD; Pavkov, KL; Donofrio, DJ; Gralla, EJ; Swenberg, JA. (1983). Carcinogenicity of formaldehyde in rats and mice after long-term inhalation exposure. Cancer Res 43: 4382-4392.

Krzyzanowski, M; Quackenboss, JJ; Lebowitz, MD. (1990). Chronic respiratory effects of indoor formaldehyde exposure. Environ Res 52: 117-125. http://dx.doi.org/10.1016/S0013-9351(05)80247-6

NRC (National Research Council). (2011). Review of the Environmental Protection Agency's draft IRIS assessment of formaldehyde (pp. 1-194). Washington, DC: The National Academies Press. http://dx.doi.org/10.17226/13142

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Taskinen, HK; Kyyronen, P; Sallmen, M; Virtanen, SV; Liukkonen, TA; Huida, O; Lindbohm, ML; Anttila, A. (1999). Reduced fertility among female wood workers exposed to formaldehyde. Am J Ind Med 36: 206-212. http://dx.doi.org/10.1002/(sici)1097-0274(199907)36:1<206::aid-ajim29>3.0.co;2-d

Venn, AJ; Cooper, M; Antoniak, M; Laughlin, C; Britton, J; Lewis, SA. (2003). Effects of volatile organic compounds, damp, and other environmental exposures in the home on wheezing illness in children. Thorax 58: 955-960. http://dx.doi.org/10.1136/thorax.58.11.955

Woutersen, RA; van Garderen-Hoetmer, A; Bruijntjes, JP; Zwart, A; Feron, VJ. (1989). Nasal tumours in rats after severe injury to the nasal mucosa and prolonged exposure to 10 ppm formaldehyde. J Appl Toxicol 9: 39-46. http://dx.doi.org/10.1002/jat.2550090108